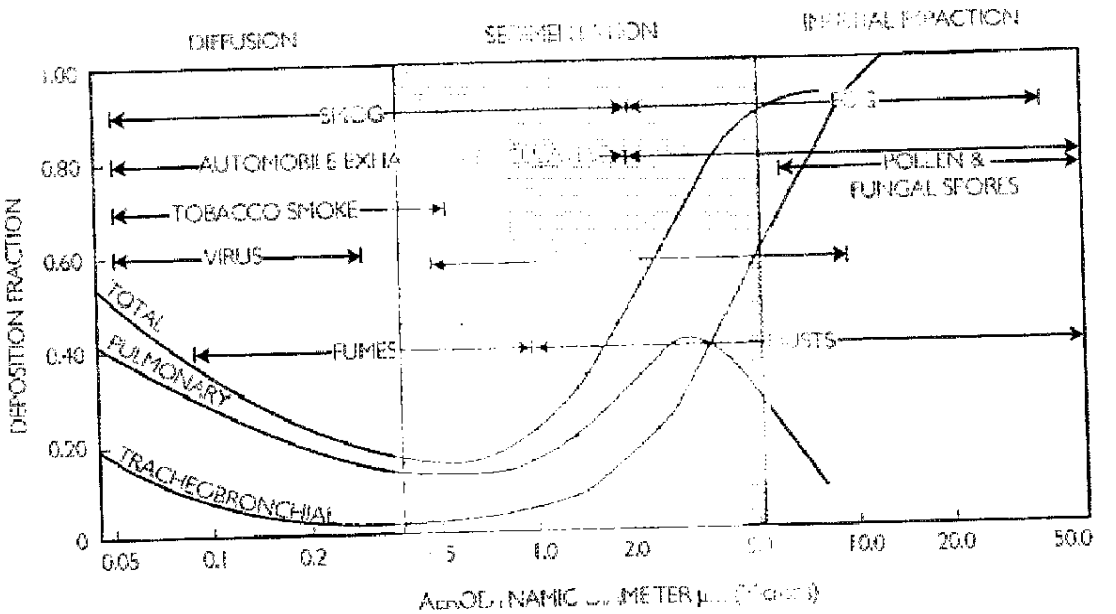


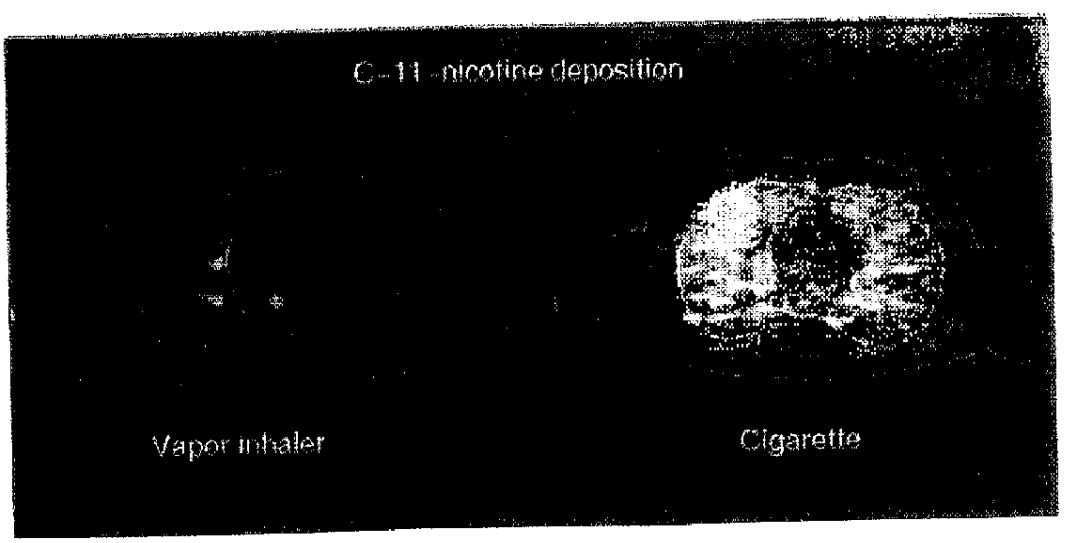
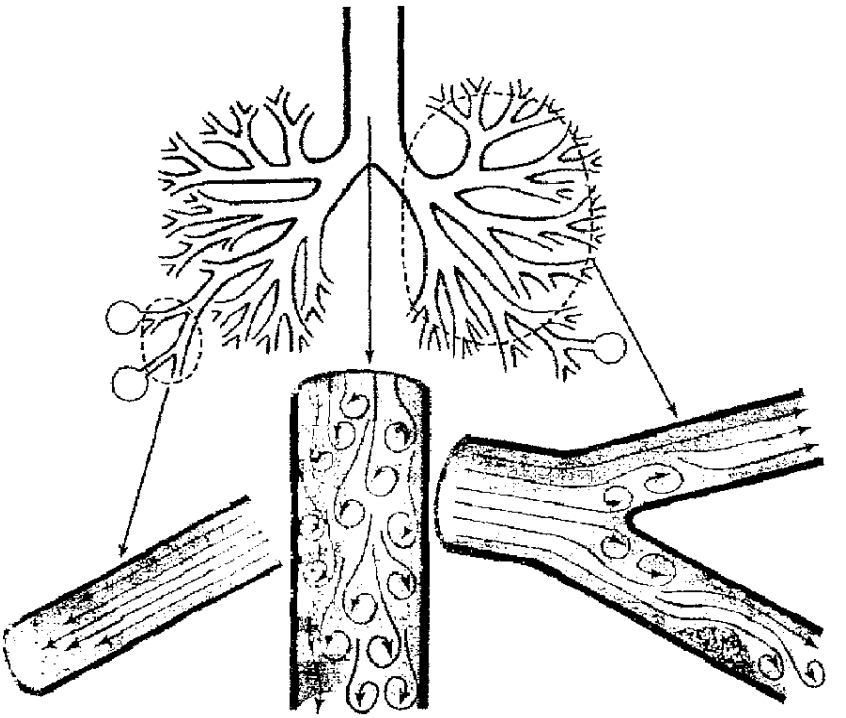


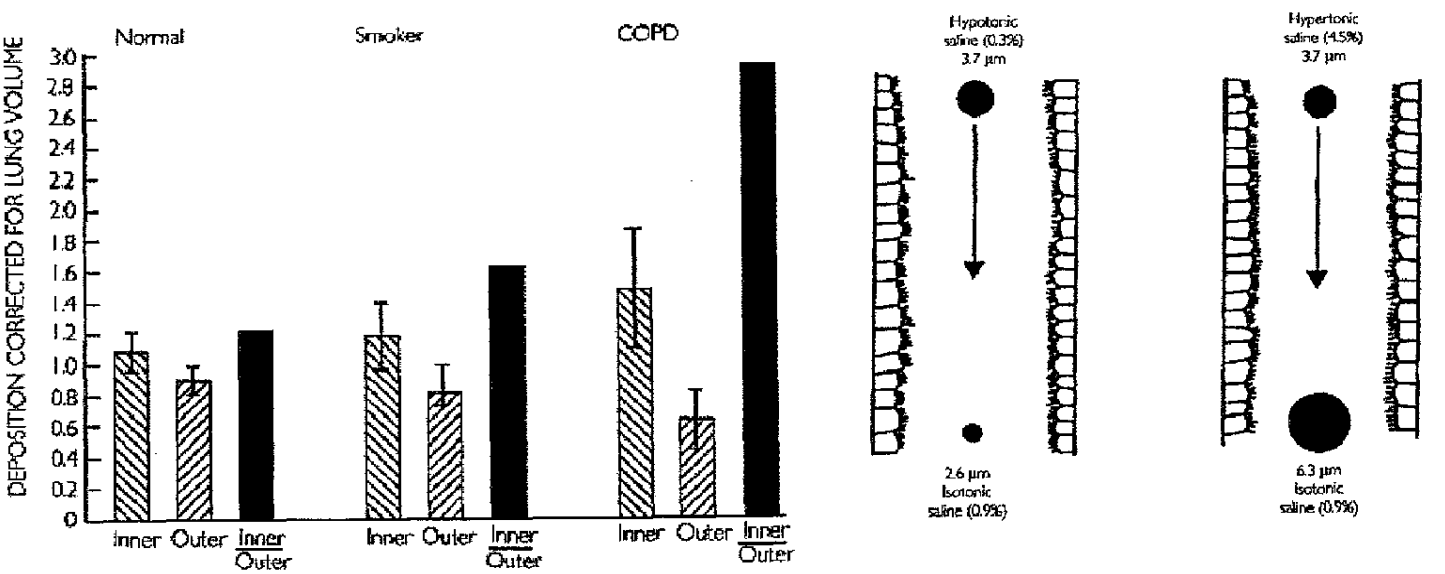
Fig. 1. [illegible] inhalation of ^{11}C [illegible], average [illegible] minutes. [illegible] shows [illegible] emission [illegible] the [illegible] lungs is seen [illegible]



Laminar flow occurs mainly in small peripheral airways where rate of airflow through any airway is low. Driving pressure is proportional to gas viscosity

Turbulent flow occurs at high flow rates in trachea and larger airways. Driving pressure is proportional to square of flow and is dependent on gas density

Transitional flow occurs in larger airways, particularly at branches and at sites of narrowing. Driving pressure is proportional to both gas density and gas viscosity



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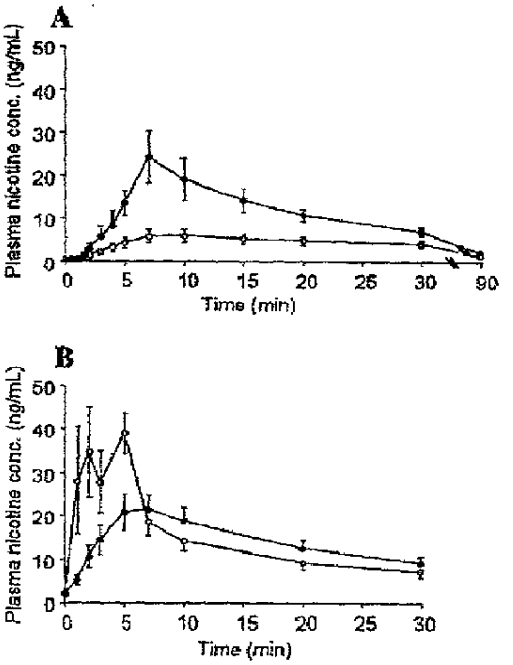


Fig. 1 A Mean ± SEM arterial (○) and jugular venous (●) nicotine concentrations after using one inhaler for 5 min ($n = 7$). B Mean ± SEM arterial (○) and jugular venous (●) nicotine concentrations after smoking one cigarette over 5 min ($n = 7$). Please note that the arterio-venous difference is reversed for the inhaler relative to the cigarette

Table I. Total organ radioactivity in percent of released dose

Organ	*Vapor inhaler (%)*	*Cigarette (%)*	*Time (min)*
Lung maximum	5.1	14	7* resp. 1.5†
Lung	4.0	3.3	15
Heart	0.4	0.4	15
Bronchi	7.0	0.7	15
Esophagus	18	0.6	15
Oral cavity	36	0.7	19
Oral cavity	14	0.4	49
Stomach	18	1.6	27
Stomach	14	2.1	60

*Inhaler.
†Cigarette.

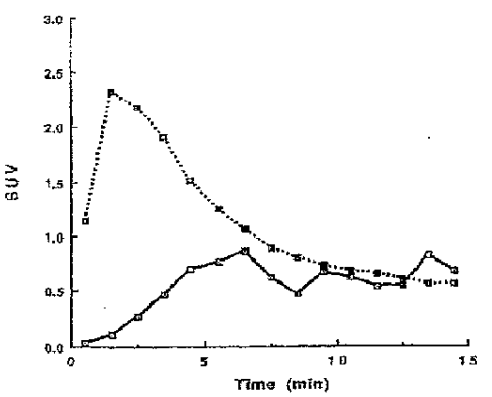


Fig. 2. Radioactivity in lung tissue after inhalation of ^{11}C-nicotine. Tissue radioactivity corrected for contribution from large bronchi and blood. A markedly higher initial lung deposition is observed for cigarette smoking compared with use of the vapor inhaler. *Solid line*, Vapor inhaler; *broken line*, cigarette. SUV, Standardized uptake value (See text).

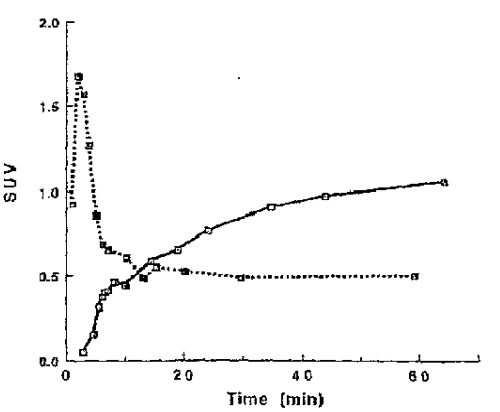


Fig. 3. Radioactivity in arterial blood after inhalation of ^{11}C-nicotine. With the vapor inhaler a gradual increase of blood radioactivity is seen. With the cigarette a sharp rise is noted to a maximum concentration within 2 minutes after the sta

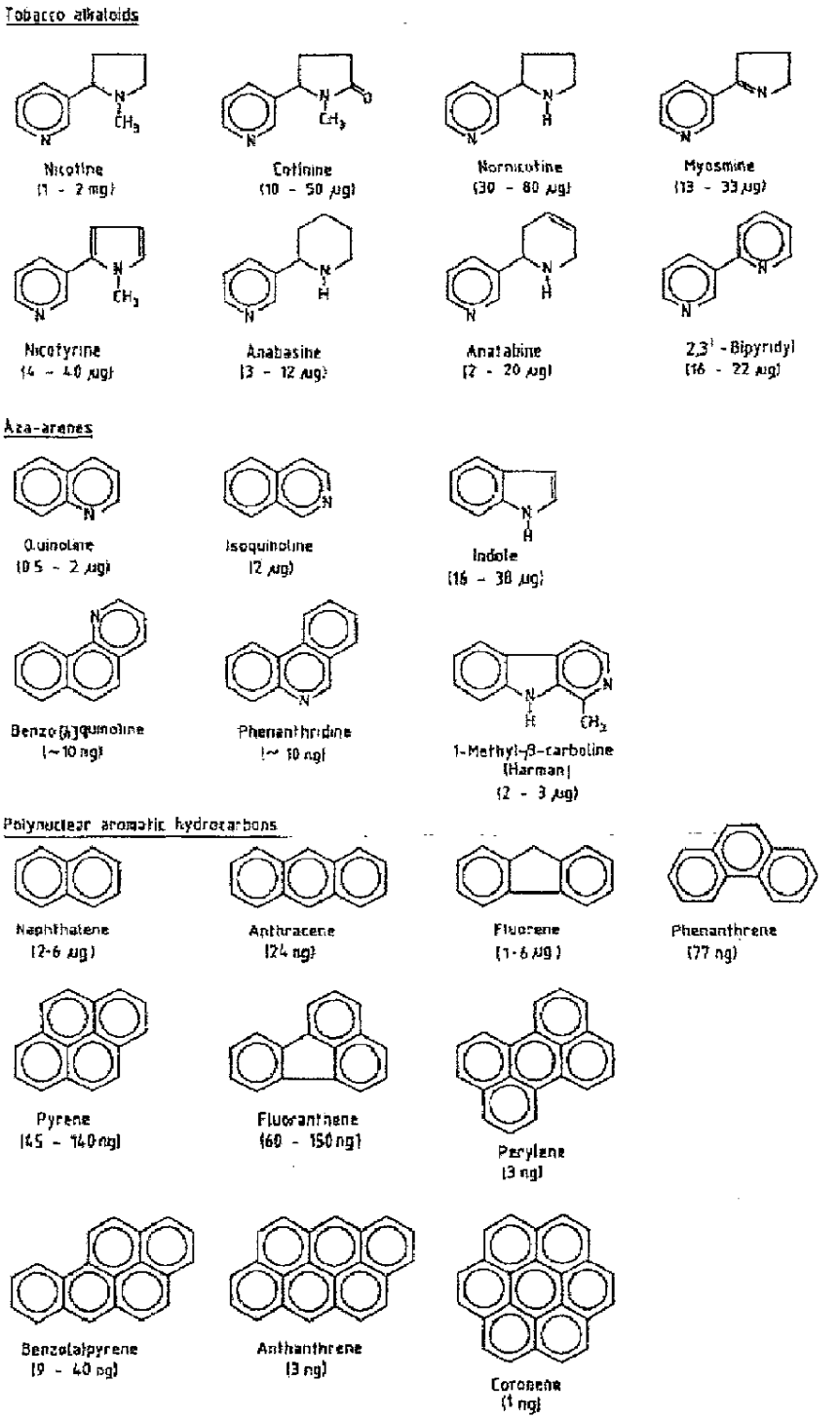
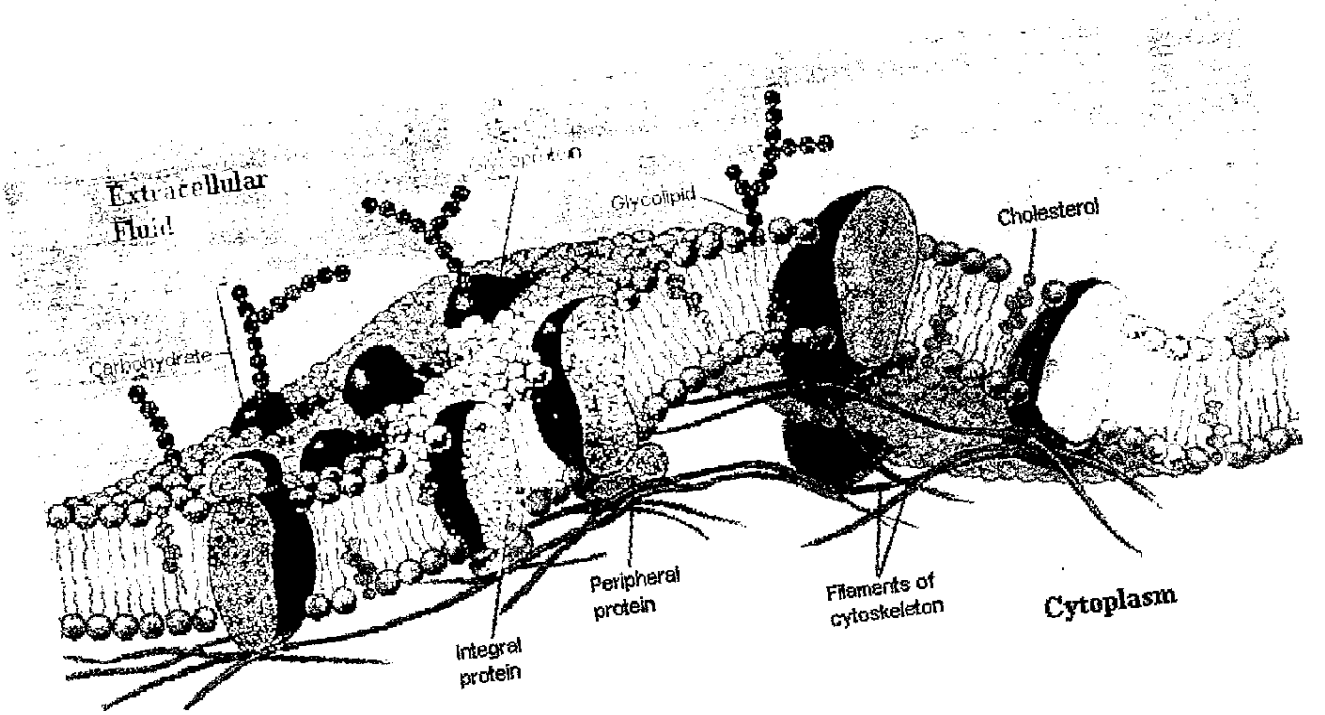


Fig. 12.12 Structures of some smoke components (and typical mainstream yields from plain cigarettes).



Passage of Drugs across cell membranes

Characteristics of Drug Molecules that Favor Drug Transport

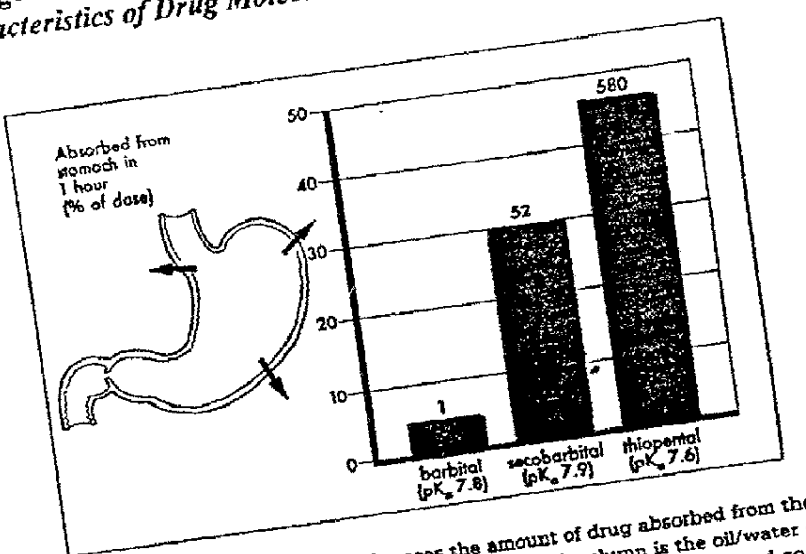
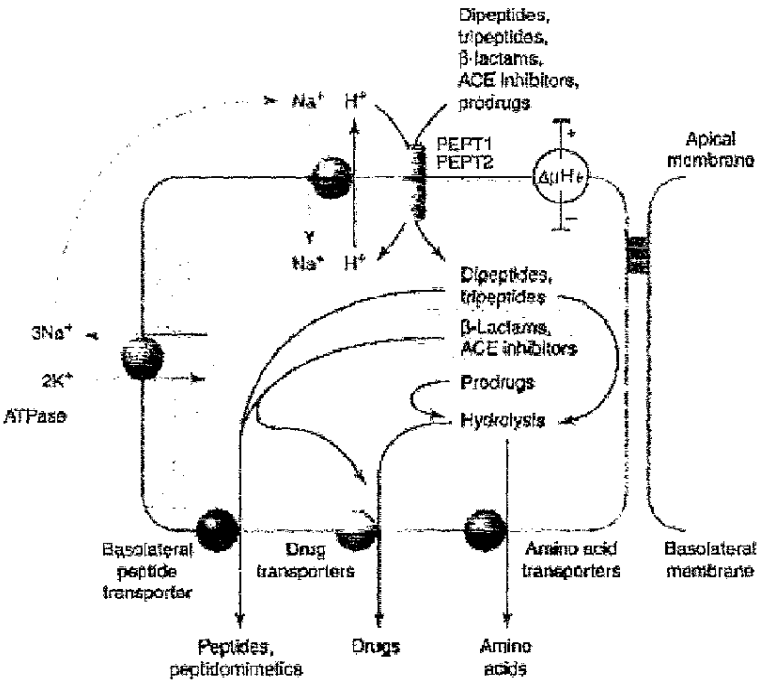


FIGURE 4-1 Increased lipid solubility influences the amount of drug absorbed from the stomach for three barbiturate compounds. The number above each column is the oil/water equilibrium partition coefficient. The compounds have roughly equivalent pK_a values and so the degree of ionization is similar for all three drugs.



TRENDS in Pharmacological Sciences

Transporter	Tissue	Localization[a]	Refs
PEPT1[b] (SLC15A1)	Small intestine	Brush border membrane of enterocytes	[53]
	Kidney	Brush border membrane of epithelial cells of the proximal tubule S1 segment	[54]
	Bile duct	Apical membrane of cholangiocytes	[55]
	Pancreas	Lysosomes of acinar cells	[56]
PEPT2 (SLC15A2)	Kidney	Brush border membrane of epithelial cells of the proximal tubule (S2 and S3 segment)	[54]
	CNS	Epithelial cells of the choroid plexus, ependymal cells and astrocytes	[57,42]
	PNS	Membrane and cytoplasm of glial cells	[58]
	Lung	Apical membrane of bronchial and tracheal epithelial cells, membrane and cytoplasm pneumocytes type II	[59]
	Mammary gland	Epithelial cells of the glands and ducts	[60]
	Spleen, colon, pancreas	-	[41]

ClinPharm 101

Absorption, Distribution Metabolism and Excretion

Objectives:

1) Understand pulmonary physiology particularly as it relates to uptake of cigarette smoke constituents using nicotine as a model compound.
2) List various physicochemical and biological factors affecting absorption
3) Describe various mechanisms of uptake of compounds through the pulmonary epithelium.
4) Explain clearance concepts as they relate to hepatic and renal elimination.
5) Discuss various metabolic processes that occur within the pulmonary region as well as hepatic and/or other organs.

Pulmonary Anatomy and Physiology – The Basics

Anatomy –

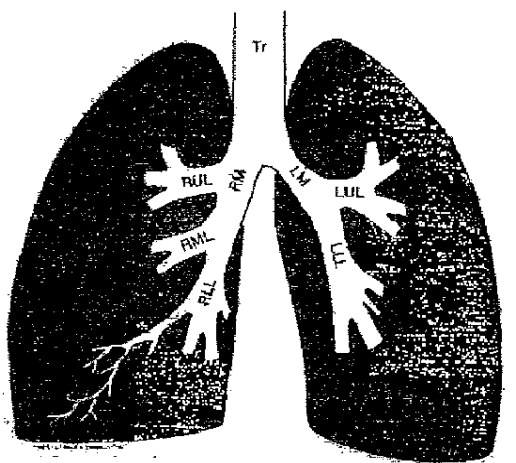


Figure 1-1 — Schematic diagram of airway branching. Tr = trachea; RM = right mainstem bronchus; LM = left mainstem bronchus; RUL = right upper lobe bronchus; RML = right middle lobe bronchus; RLL = right lower lobe bronchus; LUL = left upper lobe bronchus; LLL = left lower lobe bronchus.

Pathway for airflow

- Mouth or nose → Oropharynx or nasopharynx → Larynx → Trachea
- The bronchi, *conducting airways*, divide approximately 15 to 20 times down to the level of terminal bronchioles

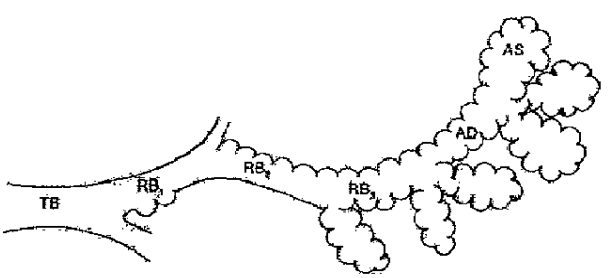
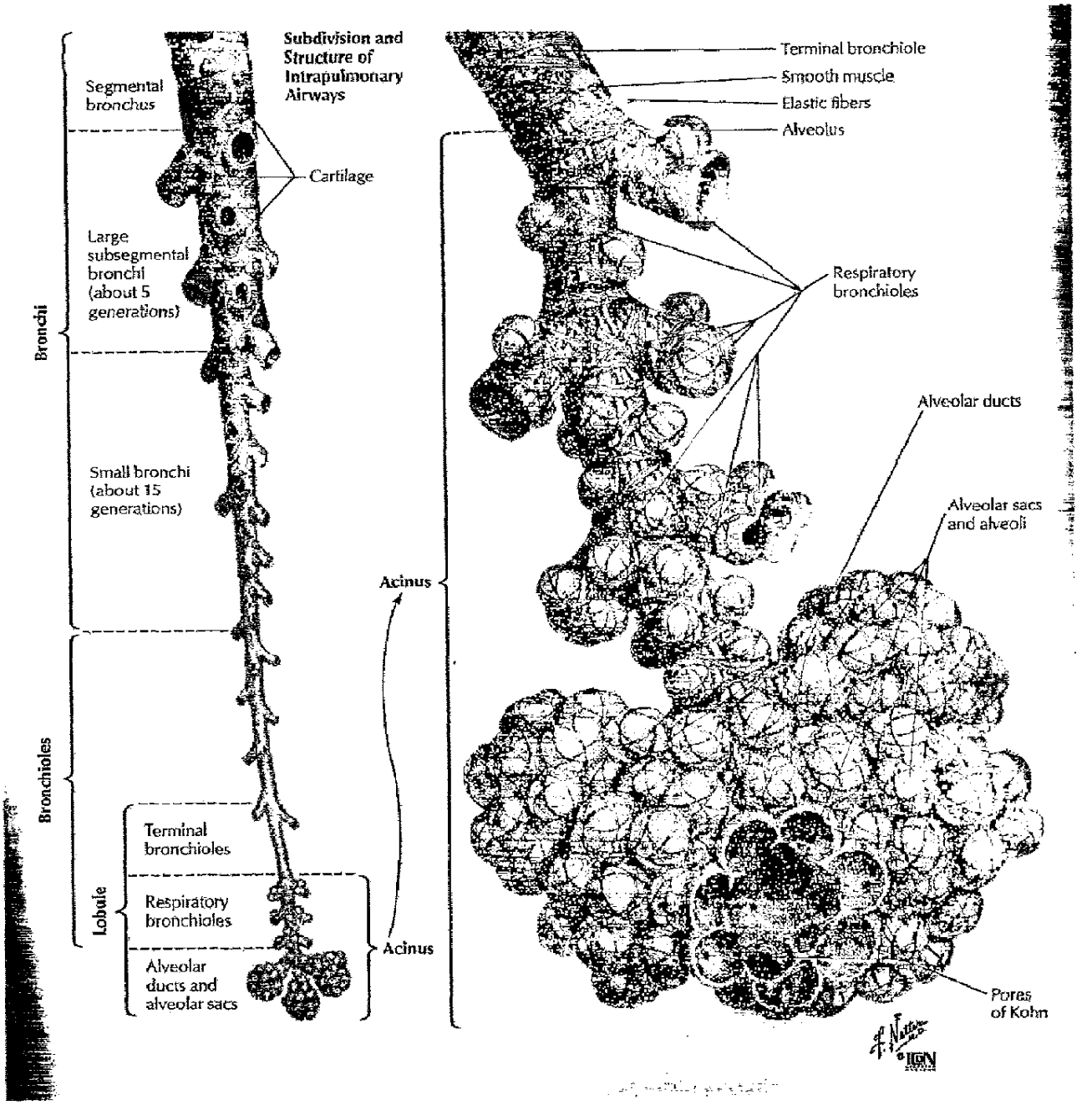


Figure 4-1 — Schematic diagram of the most distal portion of the respiratory tree. Each terminal bronchiole (TB) supplies several generations of respiratory bronchioles (RB, through RB_3), which have progressively more respiratory (alveolar) epithelium lining their walls. Alveolar ducts (AD) are entirely lined by alveolar epithelium, as are alveolar sacs (AS). Region of lung distal to and supplied by terminal bronchiole is termed *acinus*. (From Thurlbeck WM: Chronic obstructive lung disease. *In* Sommers SC (ed): Pathology Annual, Vol 3. New York, Appleton-Century-Crofts, 1968.)

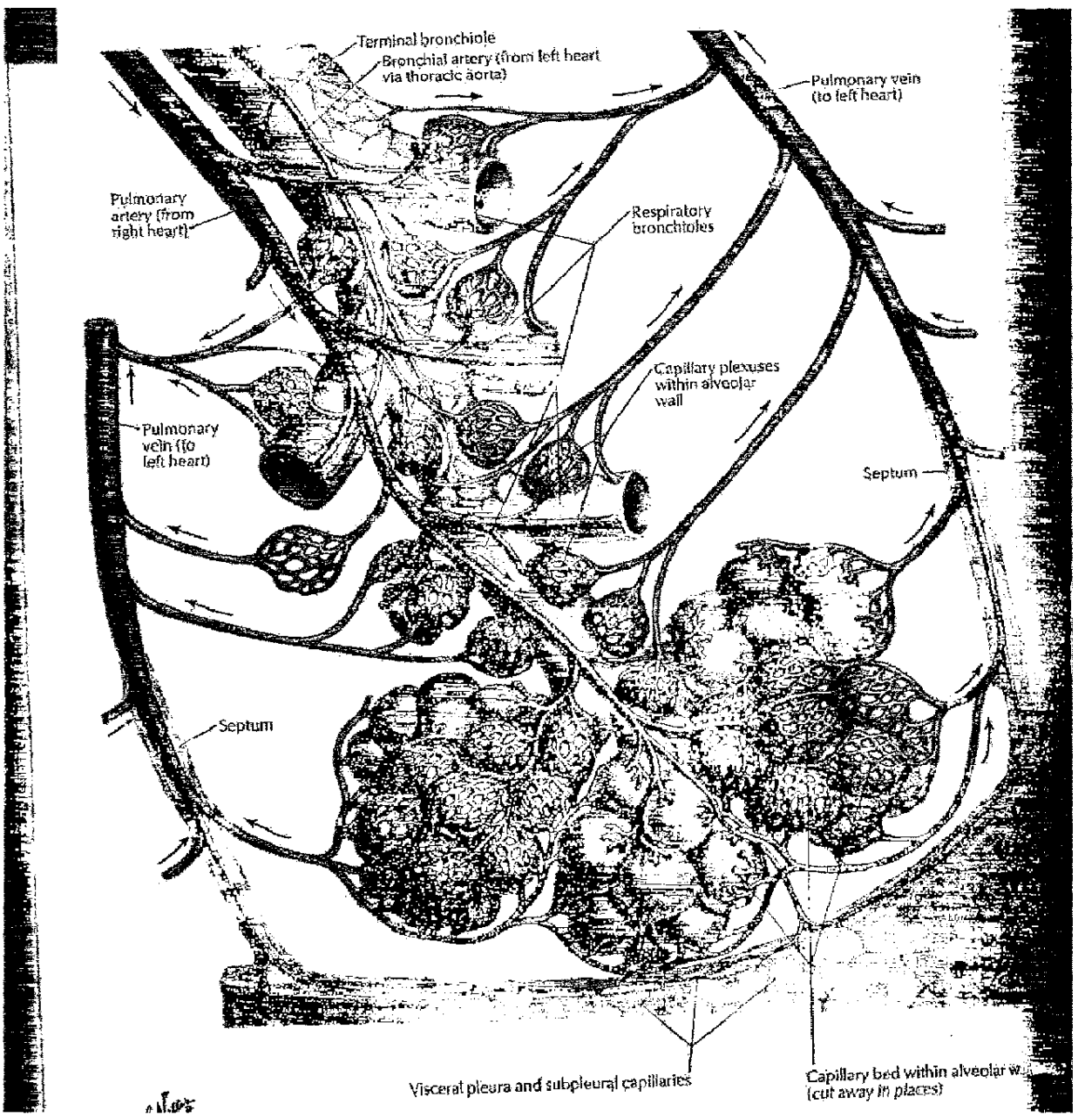
- Beyond terminal bronchioles further divisions include the respiratory bronchioles, the alveolar ducts and the alveoli, *acinus or terminal respiratory unit.*



Generation		Diameter (cm)	Length (cm)	Number	Total cross-sectional area, cm_2
Conducting zones: Trachea	0	1.80	12.0	1	2.54
Bronchi	1	1.22	4.8	2	2.33
	2	0.83	1.9	4	2.13
	3	0.56	0.8	8	2.00
Bronchioles	4	0.45	1.3	16	2.48
	5 ↓ 16	0.35 ↓ 0.06	1.07 ↓ 0.17	32 ↓ 6×10^4	3.11 ↓ 180.0
Transitional and respiratory zones: Terminal bronchioles	17				
Respiratory bronchioles	18				
	19	0.05	0.10	5×10^5	10^3
Alveolar ducts	20				
	21				
	22				
Alveolar sacs	23	0.04	0.05	8×10^6	10^4

300 million alveoli in lung

- Adult human lung has ~ 300 million alveoli
- Surface area for gas-exchange provided by the alveoli is enormous (~size of tennis court)
- *Pulmonary Capillary Network*
    - Blood arrives at the lungs via the pulmonary artery
    - Courses through a widely branching system of smaller pulmonary arteries and arterioles to the capillary network
    - Capillaries allow red blood cells to flow through in single file only
    - This facilitates efficient gas-exchange between each cell and alveolar gas



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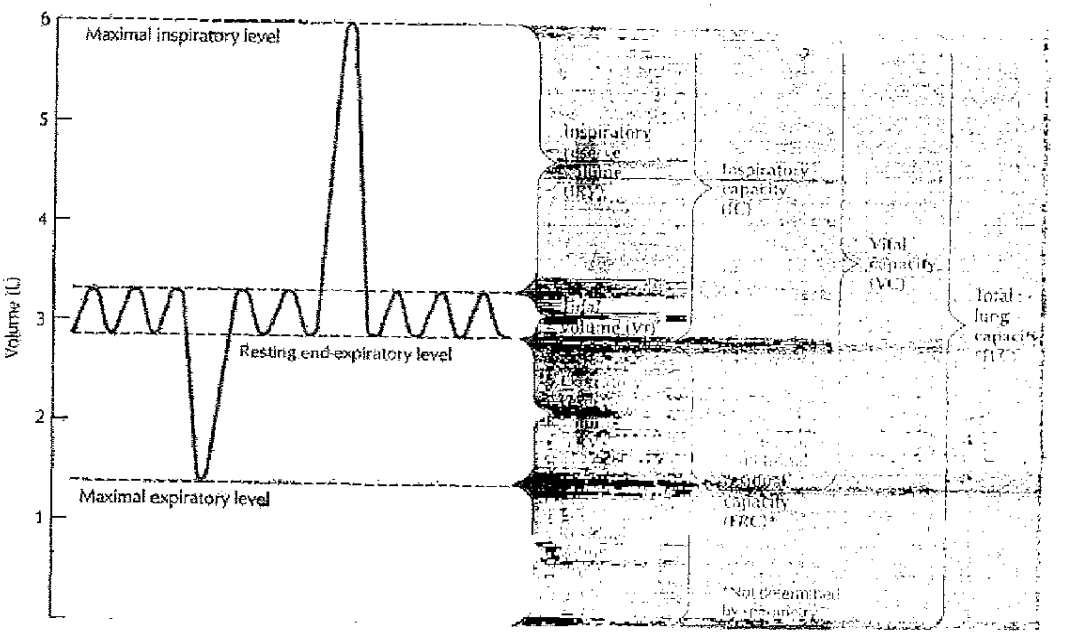
Physiology

- *Functional Residual capacity (FRC) –*
  - The lung volume at the normal resting end-respiratory position of the respiratory system.
  - At FRC, the inward elastic recoil of the lung is balanced by the outward elastic recoil of the chest wall.



- *Total lung capacity (TLC) –*
  - The volume of gas within the lungs at the end of a maximal inhalation.
  - At this point the lungs are stretched well above their resting position and even the chest wall is stretched beyond its resting position.

- *Residual volume (RV) –*
  - The volume remaining after maximum exhalation.
  - With age or with disease of the airways, further expulsion of gas during expiration is limited, not by the outward recoil of the chest wall but rather by the tendency for airways to close during expiration and for gas to be trapped behind the closed airways.

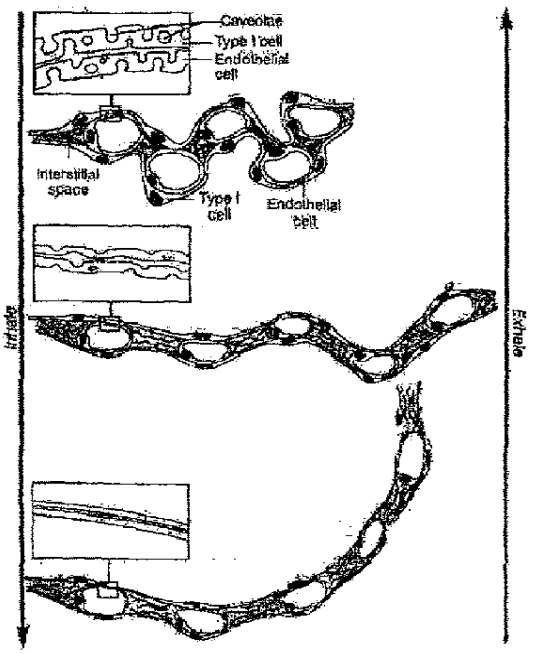
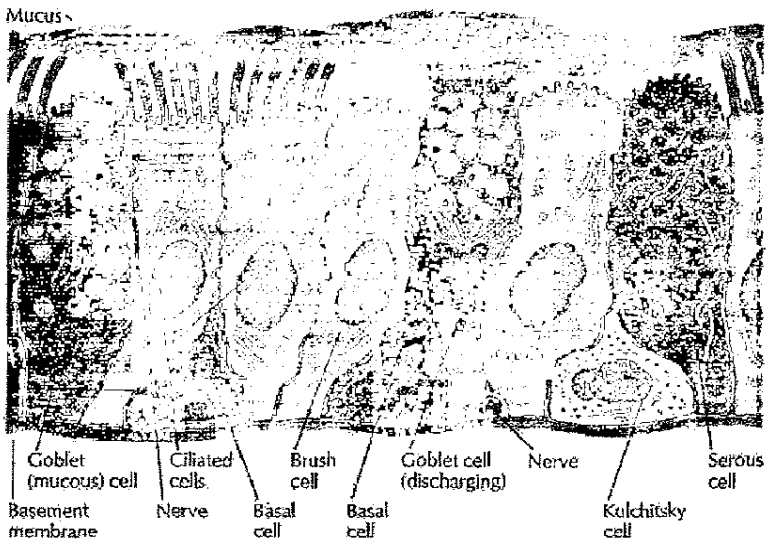
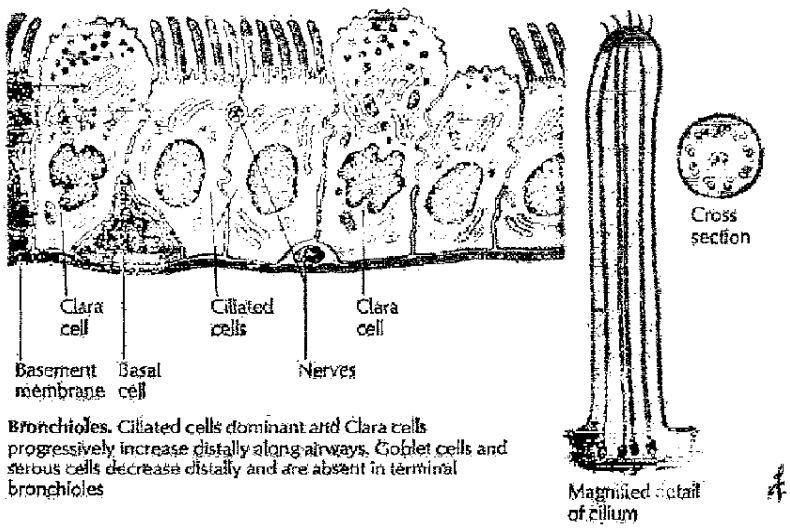


Fig. 8. During exhalation the walls (septa) of the alveoli collapse below functional reserve capacity like an accordion. During full inhalation the septal walls stretch and caveolae may be incorporated into new surface plasma membrane (inset). Presumably the same phenomenon occurs in capillary endothelium during high volume blood flow.

- *Tidal Volume (Vt) = Dead space volume (Vo) + Alveolar volume (Va)*
  - At rest, a normal person typically breathes approximately 500 ml of air per breath
  - Frequency of 12-16 times per minute
  - Ventilation of 6-8 L/min (*minute ventilation*)
  - All of Vt is not used entirely for gas exchange. A portion stays in the conducting airways and does not reach the distal part of the lung (Vo) ~150 mL.
  - Va is the Volume reaching the gas-exchanging portion of the lung



Trachea and large bronchi. Ciliated and goblet cells predominant, with some serous cells and occasional brush cells and Clara cells. Numerous basal cells and occasional Kulchitsky cells are present

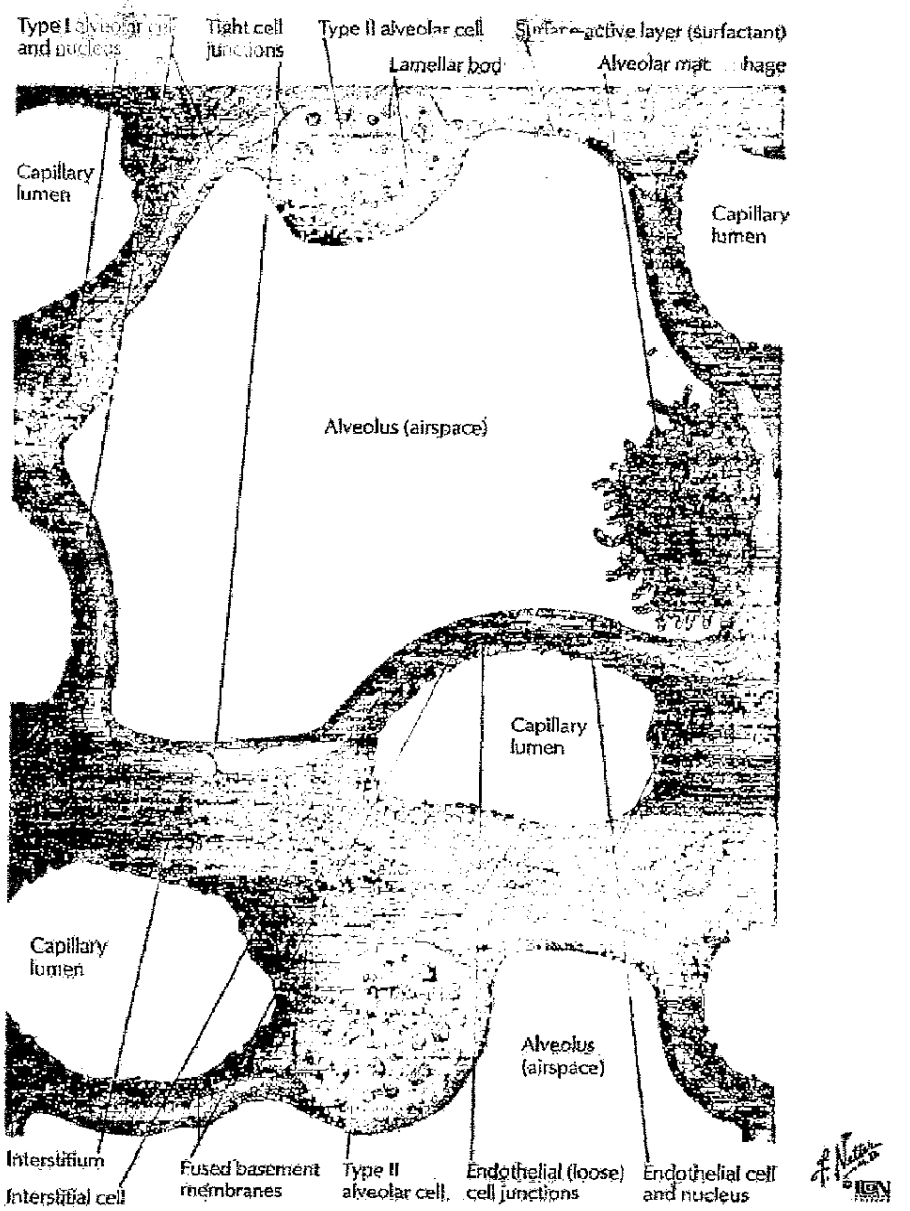


Bronchioles. Ciliated cells dominant and Clara cells progressively increase distally along airways. Goblet cells and serous cells decrease distally and are absent in terminal bronchioles

BARRIERS TO ABSORPTION IN THE LUNG

Surfactant -

- Airway and alveolar surface liquids are coated with at least a monolayer of highly **surf**ace **act**ive ag**ents**.
- The fatty acid tails of the surfactant lipids project into the air.
- The lungs surfactant reduces the surface tension of lung surface liquid.



- The monolayer of insoluble phospholipids (lung surfactant) greets any foreign macro-molecule inhaled into the lung and potentially compromises the dissolution of the substance into the surface liquid and its subsequent absorption by inducing aggregation, which could enhance engulfment and digestion by the airspace macrophages.

Surface lining fluid –

- Immediately below the molecular layer of lung surfactant lies the epithelial surface fluid through which particles must diffuse to get to the epithelial cell layer.
- This fluid acts as a reservoir for lung surfactant and appears to contain many of the components of plasma.
- At the conducting airways this fluid is a relatively thick mucus-containing airway fluid that moves constantly towards the trachea with ciliary activity.
    - Averages about 5-10 μm thick
    - Mucociliary surface velocity ~ 1-10 mm/min
- This is distinct from the thin alveolar fluid which contains no mucus and is not pushed by cilia.
    - 0.05-0.08 μm thin, but may be several microns thick in pooled areas and as thin as 15 -20 μm
- Ion transport by the pulmonary epithelium regulates the volume and composition of the surface liquids.
- pH, osmolality, ions, proteins, lipids and other constituents of the lining fluids play an important role in the composition and volume of this lining.
- Total lung surface fluid volume in humans ranges from about 15-70 ml.

Epithelium -

- The most significant barrier to absorption.
- Monolayer everywhere except in the trachea
- The cells of the airway epithelium (thick columnar cells) are very different than those of the alveolar epithelium (thin and broad cells)
- There are over 60 cell types in the lung
    - Airway epithelium has at least 4 major cell types
        - Basal cell (the progenitor cell)
        - Ciliated cell
        - Goblet cell
        - Clara cell
    - Alveolar epithelium is composed of only two major cell types
        - Extremely broad and thin Type I cell
        - Small compact Type II cell (from which the Type I cell is thought to arise)

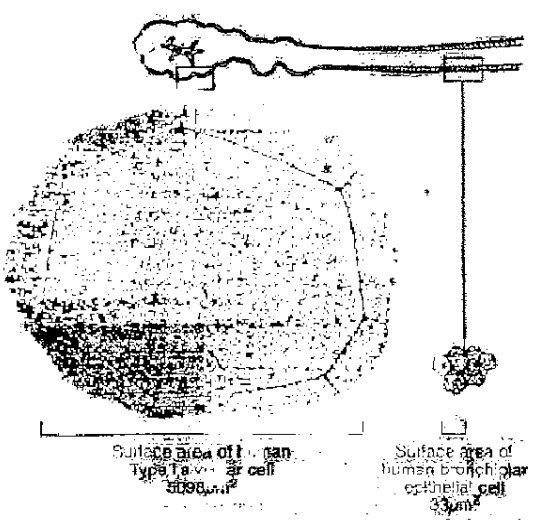


Fig. 4. Alveolar Type I cells have very large surface are compared with airway cells.

- The pattern of cells in the alveoli is a cobblestone pattern (i.e. ~2 Type II cells for every Type I cell and one macrophage for every 8 Type I cells)

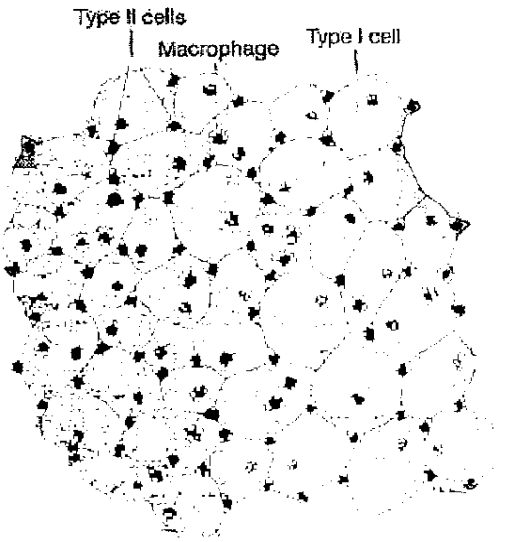


Fig. 5. If a single alveolus could be flattened, it might look like this. The average human alveolus has a surface area of 206 900 μm^2 and is covered by 40 Type I and 67 Type II cells. Cells drawn to rough scale (from [19,21,22]).

Interstitium and basement membrane

–

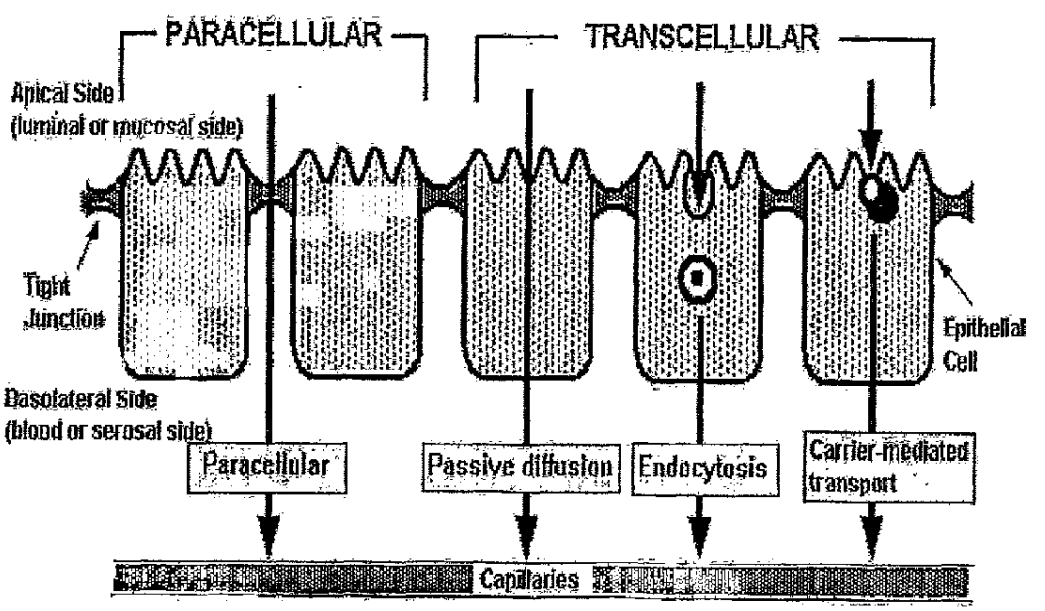
- The interstitium is the extracellular and extravascular space between cells in the tissue.
- For a molecule to be absorbed from the air spaces to the blood it must pass through the interstitium.
- Within the interstitium are fibroblasts, tough connective fibers (i.e. collagen fibers and basement membranes which serve as the structural framework on which cells of the lung are mounted).
- The interstitial fluid slowly diffuses and percolates through the tissue.
- This fluid is drained as lymph in lymphatic vessels, which gradually transport the fluid back to the blood.
- The interstitium is analogous to a sophisticated chromatography column (this one is for Robin and Shixia ☺) with a fraction of water and solutes bound to the fibrous gel-like structures of the extracellular matrix, plasma proteins and most solutes are thought to diffuse relatively unhindered through it.
- The epithelial and endothelial (capillary) cells are attached to a tough but thin layer of interstitial fibrous material known as the basement membrane.
- The epithelial cells are attached to one basement membrane and the capillary cells (endothelium) are attached to another. Where these two cell layers come in contact (which is frequent throughout the alveoli) their basement membranes fuse to form one common basement membrane.
- The role of the basement membrane and that of the interstitium in absorption is uncertain.

Vascular endothelium -

- The final barrier to systemic absorption is another monolayer of cells that make up the walls of small blood and lymph vessels.
- The permeability of this second cell barrier varies with the type of blood vessel but even the tightest regions are thought to be more permeable to molecules than pulmonary epithelium.
- The surface area of a pulmonary endothelial cell is about 1/5th the size of the Type I cell.
- *Lymphatics*
    - "Backdoor" pathway.
    - Fluid and solutes that slowly seep of the blood system into tissues are recycled back to the circulation through a system of vessels and filters (lymph nodes) known as the lymphatic system.
    - Lymphatic endothelia have large open flaps in their walls which will let micron-sized particles (i.e. fat droplets, lipoproteins, bacteria, viruses and immune cells) freely pass.
    - Fluid flow is normally very slow relative to blood (1/500th velocity of blood) but the protein concentration is 60-70% that of plasma.

MECHANISMS OF ABSORPTION

- Lung is not particularly permeable to small molecules
- However its tremendous surface area, very low surface fluid volume, very thin diffusion layer, sluggish cell surface clearance and anti-protease defense there is still reasonably high bioavailability
- For a variety of low and high molecular weight solutes, >90% of the alveolar absorption "barrier" is in the epithelium.
- Macromolecule absorption from the lung is inversely related to molecular mass over the range of 1-500 kDA – smaller molecules diffuse faster than



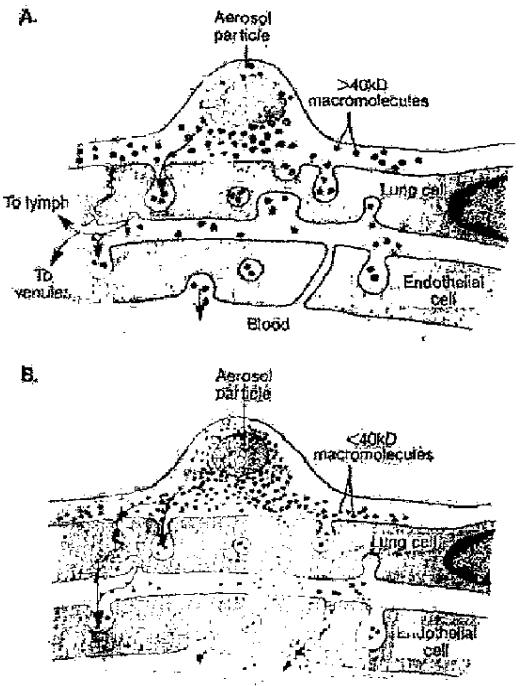


Fig. 15. Models for the absorption of macromolecules across alveolar Type I cells. (A) Molecules larger than ~40 kDa may be absorbed by transcytosis and then enter blood either via transcytosis in the capillary, drainage into lymph or absorption through the leaky junctions of capillaries or post capillary venules. (B) Molecules smaller than about 40 kDa may directly enter the blood primarily via the tight junctions of both the Type I cell and the capillary. Transcytosis may be a minor route of transport for these small peptides. Note that pericellular junctions are not shown, nor are holes left by dying or injured cells.

large molecules.

- Inhaled and instilled macromolecules >40 kDA (i.e. 5-6 nm diameter which includes almost all plasma proteins) are slowly absorbed over many hours from the airspaces
- Peptides and proteins <40 kDA (i.e. <5-6 nm in diameter) can rapidly appear in blood following instillation or inhalation into the airways.
- Most cytokines (18-22 kDA ~3-4 nm in diameter), insulin (5.7 kDA, 2.2 nm in diameter) and many small peptides are absorbed rapidly and peak in the blood in 5-90 mins in humans.

- Paracellular transport -
  - Usually thought to occur through the junctional complex between two cells by passive diffusion
  - It is also believed that there various pores that allow passage of molecules, e.g. small pores corresponding to the thin slits between the cells, and large pores that represent vesicular transport (transcytosis) or space created by senescent or injured cells.
  - The small pores in the alveoli and trachea have estimated diameters of about 1-5 nm.
  - Pulmonary epithelial cells are "tight" but the endothelial cells are thought to be leaky.
  - There are ~ 60 miles of cell junction in human airways and >2000 miles in the alveolar region
  - Epithelial defects (big pores) occur when cells are injured or die by apoptosis creating a big gap till new cells replace this denuded region.

Passive Diffusion

Based on Fick's Law of Diffusion

$$J = K \times D \times \frac{dc}{dx}$$ Equation 1

Where
J is the flux per unit area,
D is the diffusion coefficient in the membrane,
K is the partition coefficient of the solute,
dc is the concentration gradient across the membrane, and
dx is the thickness of the membrane that the solute has to travel.

Equation 1 can also be written as:

$$J = P \times dc$$ Equation 2

where,

$$P = \frac{D \times K}{dx}$$ Equation 3

$$TotalFlux = J_{total} = J_{Unionized} + J_{Ionized}$$
Equation 4

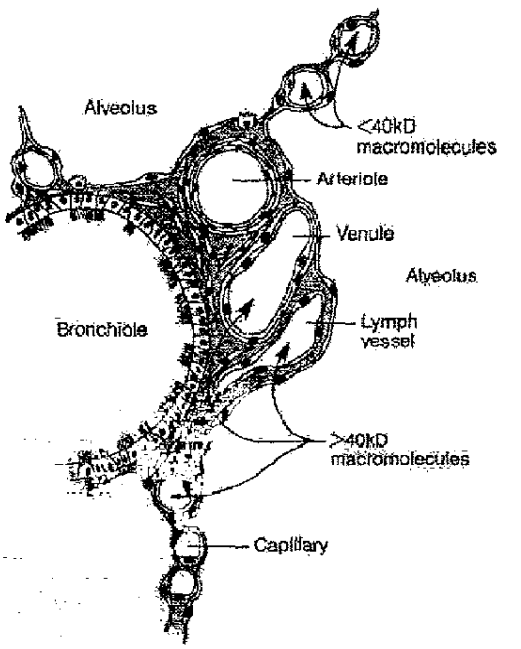
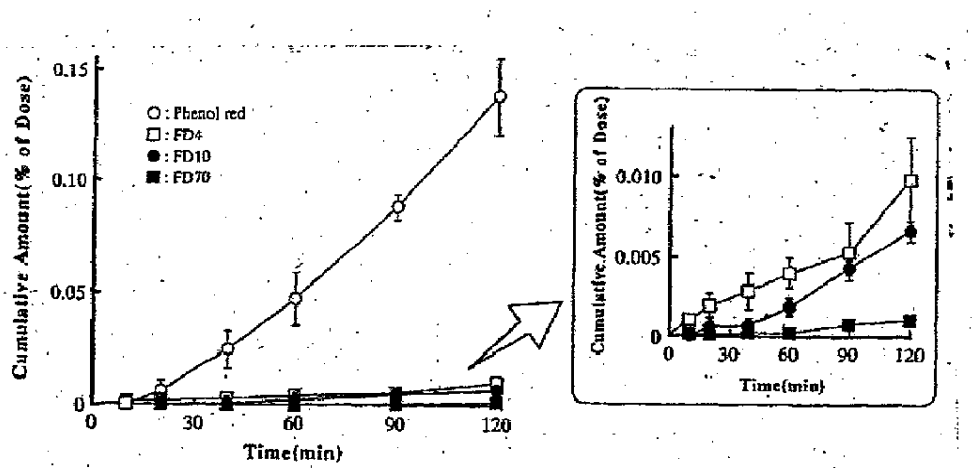


Fig. 16. Model showing potential pathways of macromolecule absorption from alveoli. Proteins larger than 40 kDa are probably absorbed into the blood primarily through the lymph and venules. Macromolecules smaller than 40 kD may be absorbed directly into the blood across the septal wall.



$$DC = \frac{P_{unionized}}{P_{ionized}}$$ Equation 5

where, DC = Discrimination Coefficient and is typically in the range 10^6 to 10^8

Transcellular transport -

- Occurs without disrupting the barrier function of the plasma membrane or its electrochemical potential on either side of the cell.
- In the endothelium this occurs through non-coated vesicles called caveolae (~40 nm of opening diameter and internal diameter of 50-100 nm).
- These calveolar vesicles are also found in Type I epithelial cells and are believed to be involved in transport.
- Receptor mediated transcytosis also occurs in the lung
- Albumin receptor on alveolar is responsible for a slow but steady absorption of albumin

Active/Carrier Mediated Absorption

Saturable (Capacity limited) Michaelis-Menten transport

$CT + S_{out} \leftrightarrow CT\text{-}S \rightarrow S_{in}$

$$\frac{dS_{in}}{dt} = v = \frac{V_{max} \times [S_{out}]}{K_m \times [S_{out}]}$$ Equation 6

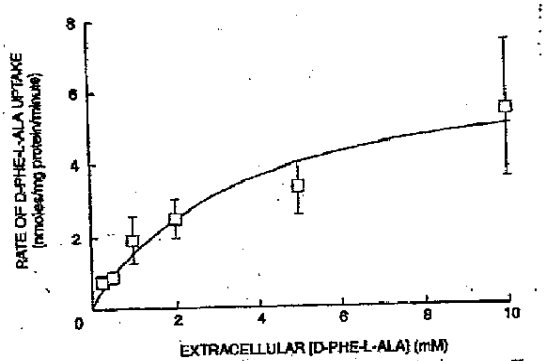


Fig. 2. Concentration dependence of D-Phe-L-Ala uptake into type II pneumocytes. Freshly isolated type II cells were incubated for 30 s at 37°C with Krebs-Ringer containing varying concentrations of D-Phe-L-Ala. Data are fitted to the Michaelis-Menten equation (excluding the 10 mM point), giving an apparent Michaelis-Menten constant (K_m) of 3.4 mM and a maximum velocity (V_{max}) of 7.9 nmol·mg protein^{-1}·min^{-1}. Values are means ± SE; $n = 3$.

or in flux terms, Active absorption can be shown as:

$$J = \frac{J_{max} \times C}{K_m + C}$$ Equation 7

Where
J is the flux for a substrate concentration of C,
Jmax is the maximum flux, and
Km is the concentration of substrate when J is 50% of the maximum (Jmax).

- Pulmonary macrophages are adapted to avidly engulfing exogenous particulate matter that might deposit in the lungs.

ALTERED PULMONARY ABSORPTION IN SMOKERS

- Cigarette smoke contains several compounds that are thought to stimulate alveolar macrophages and polymorphonuclear cells to release oxidants which are thought to damage the epithelium.
- The role of the reactive oxygen species in smoke itself in this process is still not clear.
- A pack of cigarette is believed to deposit ~400 MG of material on a smoker's lung.
- Smoker's lungs are much more permeable than nonsmokers
- This enhanced permeability is reversible and returns to nonsmoking level within few days
- Primary cause of increased permeability is possibly due to damage to alveolar Type I cells adjacent to the bronchioalveolar junction.
- The damage occurs as denudation and desquamation of cells to a density of about 1-2 µm of linear damaged surface/ 100 µm.
- The focus of damage near the bronchioalveolar junctions may be the result of high deposition o particulates that occurs at that site.
- Smoking also markedly increases the number of alveolar macrophages which clear deposited material by engulfment.

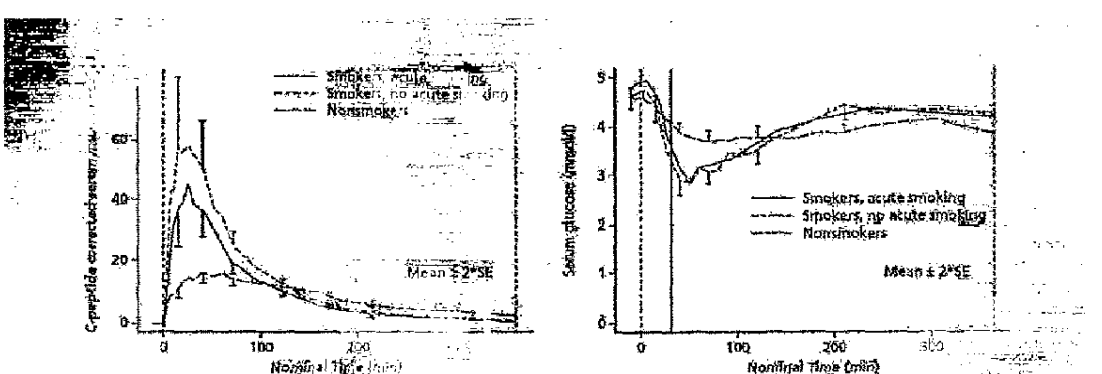


Figure 2—Mean exogenous serum insulin curves during pri for smokers and nonsmokers. NB: Intravenous glucose infusion is initiated if a subject's blood glucose rea 2.0 mg/l. The ve ute at min marks the time of the first glucose infusion.